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# Clinicopathological Features of Multiple Primary Gastric Carcinoma

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The clinicopathological features of multiple primary gastric carcinoma in 107 patients who had undergone gastrectomy between 1972 and 1992 were studied and compared with those of single gastric carcinoma in 1,456 patients. The incidence of occurrence of multiple primary gastric carcinoma was 6.8% of patients who had gastrectomy for gastric cancer. Such carcinoma was detected less often in patients <49 years of age. Dominant findings involved an elevated gross appearance, papillary or well-differentiated adenocarcinoma in the histology, and invasion to the depth of mucosa. When multiple primary gastric carcinoma was classified by main and concomitant lesions based on the stage of the disease, concomitant lesions were detected more often in the lower third of the stomach and at the distal site of main lesions located in the upper or middle third of the stomach. These results indicate that the lower third of the stomach and the distal site of the main lesion must be investigated carefully to ensure that incidental concomitant lesions are not overlooked, especially when a patient has the clincopathological features described above.


KEY WORDS: **multiple primary gastric carcinoma, clinicopathological features, main lesion, concomitant lesion**

## INTRODUCTION

Technical advances in endoscopic and radiological examination led to an increased incidence of the diagnosis of gastric carcinoma in early stages of the disease and the preoperative detection of multiple lesions. It is common to find more than one distinct type of carcinoma developing in a stomach. The incidence of multiple primary gastric carcinoma in the general patient population with gastric carcinoma is reported to be 0.83–22% [1–12]. To clarify the clinocopathological features of multiple primary gastric carcinoma, we retrospectively studied surgically treated multiple primary gastric carcinoma, in comparison to single gastric carcinoma. To ensure that small multiple carcinomas were not overlooked at surgery, we divided multiple primary gastric carcinoma into two lesions, i.e., main and concomitant lesions and the correlation between location of the two lesions was studied.

## MATERIALS AND METHODS

In the two decades from 1972 to 1992, 107 patients (6.8%) of 1,563 gastric cancer patients who had undergone gastrectomy in our department were diagnosed as having multiple primary gastric carcinoma. We inspected resected stomachs and coordinated these with histological examinations to determine the number of lesions. Multiple primary gastric carcinoma was diagnosed based on the following criteria: (1) each lesion must be pathologically proved to be malignant and (2) all lesions must be distinctly separated and must not have metastasized from another lesion [2]. The residual stomach was examined by fluoroscopy or gastrofiberscopy in all patients, except those undergoing total gastrectomy, 1 year after surgery to help prevent other carcinomas in the gastric remnant from being overlooked. Lesions with the most advanced depth of invasion in multiple primary gastric carcinoma detected in a resected specimen were defined as the "main lesion" and others defined as "concomitant lesions." If

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TABLE I. Multiple Primary Gastric Carcinoma: Incidence of Multiple Lesions

| No. of tumors | No. of patients | No. of lesions |
|---|---|---|
| 2 | 84 (78.5%) | 168 |
| 3 | 17 (15.9%) | 51 |
| 4 | 4 (3.8%) | 16 |
| 5 | 1 (0.9%) | 5 |
| 7 | 1 (0.9%) | 7 |
| Total | 107 (100%) | 247 |

TABLE II. Multiple-Lesion Combination in the Same Patient

| | Concomitant lesion | |
|---|---|---|
| | Early | Advanced |
| Main lesion | | |
| Early | 55* | — |
| Advanced | 47* | 5** |

* vs. **: $P < 0.001$.

the depth of invasion was equal, the largest lesion was determined to be the main lesion. The number of lesions were counted and the mode of combination between main and concomitant lesions was studied by classifying early and advanced gastric cancer. The accuracy of the preoperative diagnosis of multiple primary gastric carcinoma was investigated by number, size, and location of multiple lesions.

To identify the features of multiple primary gastric carcinoma, we studied the clinicopathological findings for 107 patients compared to 1,456 single gastric carcinoma patients in terms of the folowing points: (1) clinical findings: gender, age, location, and gross appearance, and (2) pathological findings: histologic type and depth of invasion. The correlation between the location of the main and concomitant lesions was studied to determine accurate treatment without overlooking concomitant lesions.

The Chi-square test was used for statistical analysis. Values of $P < 0.05$ were considered significant.

## RESULTS

### Number of Patients and Multiple Primary Gastric Carcinoma Lesions

Carcinoma lesions numbered 247 in the 107 patients (Table I). Patients with two lesions predominated (79%). Those with three lesions occurred in 16% and those with four or more lesions in about 5%. Preoperative diagnosis in 38 patients (32.7%) was correct in size, number, and site of multiple primary lesions. In the remaining 69 patients, other cancer lesions were first detected or correctly diagnosed by examination of the resected specimen.

### Mode of Multiple-Lesion Combination in Same Patients

In 55 cases, all lesions were early carcinoma and in five cases, all were advanced carcinomas (Table II). In 47 cases, both early and advanced carcinoma was observed in the same patient.

### Gender and Age

A male/female ratio showed no difference between patients with multiple primary gastric carcinoma and those with single carcinoma (Table III). Multiple primary gastric carcinoma was detected less often in patients <49 years old.

### Pathological Findings

Pathological findings for both multiple and single lesions are given in Table IV.

**Location.** Multiple lesions were detected more often in the lower third of the stomach than in the upper third. No difference was seen in the incidence of occurrence, when compared with upper, middle, and lower thirds of the stomach between multiple and single occurrence groups.

**Gross appearance.** In the multiple-lesion group, an elevated type of early gastric carcinoma was observed more frequently and types III and IV advanced gastric carcinoma were seen lesss frequently.

**Histologic type.** Papillary adenocarinoma and well-differentiated adenocarcinoma were present more often, whereas poorly differentiated adenocarcinoma was less often present in the multiple group than in the single group.

**Depth of invasion.** Most lesions in the multiple group were in the mucosa or in the submucosa. The deeper the depth of invasion, the fewer the number of multiple lesions. Mucosal cancer was demonstrated more often and serosal cancer was demonstrated less often in the multiple group.

### Correlation of Locations of Main and Concomitant Lesions

Concomitant lesions numbered 29, 45, and 66 when the main lesion was located in the upper, middle, and lower thirds of the stomach (Table V). The ratio of main to concomitant lesions was almost the same in the three regions (upper third: 21/29, middle third: 36/45, lower third: 50/66). When we compare the incidence of occurrence in the upper third of the stomach, concomitant lesions (14/140) was almost half that of main lesion (21/107). The sites of the main and incidental concomitant lesions are shown in Table VI. For a main lesion in the upper or middle third of the stomach, incidental concomitant lesions were observed more frequently at distal sites than at the proximal site of the main lesion. In contrast, for a main lesion located in the lower third of the stomach, concomitant lesions were more often observed at proxi-

**TABLE III. Multiple Primary Gastric Carcinoma: Gender and Age**

| | Multiple (107 patients) | Single (1,456 patients) | Significance |
|---|---|---|---|
| Gender | | | |
| male | 80 (74.8%) | 990 (68%) | NS[a] |
| female | 27 (25.2%) | 466 (32%) | NS |
| Age | | | |
| <49 yr | 17 (15.9%) | 374 (25.6%) | <0.05 |
| 50–59 yr | 28 (26.2%) | 438 (30%) | NS |
| 60–69 yr | 40 (37.4%) | 422 (29%) | NS |
| >70 yr | 22 (20.5%) | 221 (15.2%) | NS |

[a]NS = not significant.

**TABLE IV. Multiple Primary Gastric Carcinoma: Clinicopathological Findings**

| | Multiple (247 lesions) | Single (1,456 lesions) | Significance |
|---|---|---|---|
| Location | | | |
| upper third | 35 (14.2%)[a] | 253 (17.4%)[b] | NS |
| middle third | 91 (36.8%) | 554 (38.0%) | NS |
| lower third | 121 (49.0%)[a] | 649 (44.6%)[b] | NS |
| Gross appearance | | | |
| Early cancer | | | |
| elevated type | 57 (31.8%) | 136 (20.0%) | <0.001 |
| depressed type | 98 (57.4%) | 457 (67.3%) | NS |
| others | 24 (13.4%) | 86 (12.7%) | NS |
| Advanced cancer | | | |
| Borrmann I | 5 (7.4%) | 68 (8.8%) | NS |
| Borrmann II | 35 (51.5%) | 243 (31.3%) | NS |
| Borrmann III | 9 (13.2%) | 214 (27.5%) | <0.001 |
| Borrmann IV | 3 (4.4%) | 102 (13.1%) | <0.001 |
| Unclassified | 16 (23.5%) | 150 (19.3%) | NS |
| Histologic type | | | |
| papillary | 25 (10.1%) | 87 (6.0%) | <0.001 |
| well differentiated | 96 (38.9%) | 310 (21.3%) | <0.05 |
| moderately differentiated | 63 (25.5%) | 397 (27.3%) | NS |
| poorly differentiated | 46 (18.6%) | 554 (38.0%) | <0.001 |
| mucinous | 6 (2.4%) | 29 (2.0%) | NS |
| signet-ring cell | 11 (4.5%) | 79 (5.4%) | NS |
| Depth of invasion | | | |
| mucosa | 125 (50.6%) | 388 (26.6%) | <0.001 |
| submucosa | 54 (21.8%) | 310 (21.3%) | NS |
| muscularis propria | 27 (10.9%) | 150 (10.3%) | NS |
| subserosa | 24 (9.7%) | 207 (14.2%) | NS |
| serosa | 17 (6.9%) | 401 (27.5%) | <0.001 |

NS = not significant.
[a,b]$P < 0.001$.

mal sites of the main lesion. Most of 40 concomitant lesions at proximal sites of main lesions were limited to the lower or middle third of the stomach (Table V), and only seven lesions were present in the upper third.

## DISCUSSION

The incidence of multiple primary gastric carcinoma has been reported to be 0.83–22% [1–12] of patients with gastric cancer, but more commonly 4.4–9.7% [6–12] in reports after 1980 (Table VII). In these reports, multiple primary gastric carcinoma demonstrated a more common occurrence in men, with ratios from 2.6/1 to 9.5/1 and more common in patients 59–69 years old. Our study showed a male/female ratio of 3/1, but there was no difference in the ratio compared to those with single gastric carcinoma, and a smaller number of patients with multiple primary gastric carcinoma was demonstrated in those <49 years. Most authors have documented a more frequent occurrence of well-differentiated or differentiated gastric adenocarcinoma in patients with multiple

**TABLE V. Multiple Primary Gastric Carcinoma: Correlation of Locations of Main and Concomitant Lesions**

| Main lesion | Concomitant lesion | | | |
|---|---|---|---|---|
| | Upper third | Middle third | Lower third | Total |
| Upper third (n = 21)* | 4 | 12 | 13 | 29 |
| Middle third (n = 36) | 3 | 20 | 22 | 45 |
| Lower third (n = 50)** | 7 | 22 | 37 | 66 |
| Total | 14*** | 54 | 72**** | 140 |

* vs. **, *** vs. ****: $P < 0.001$.

**TABLE VI. Multiple Primary Gastric Carcinoma: Location of Concomitant Lesion†**

| Main lesion | Concomitant lesion | | | |
|---|---|---|---|---|
| | Proximal site of main lesion | Same level | Distal site of main lesion | Total |
| Upper third | 0 | 4 | 25* | 29 |
| Middle third | 9 | 11 | 25* | 45 |
| Lower third | 40* | 14 | 12 | 66 |
| Total | 49 | 29 | 62 | 140 |

† Proximal or distal site of the main lesion.
* $P < 0.001$ (proximal vs. distal).

primary gastric carcinoma. It was reported that multicentric growth of gastric cancer was associated with atrophy or intestinal metaplasia by histopathological study of surrounding gastric mucosa of multiple primary gastric cancer [11]. It is thus reasonable to assume that multiple primary gastric carcinoma tends to be well differentiated in histologic classification.

The accuracy of the preoperative diagnosis of multiple primary gastric carcinoma was low and unsatisfactory (32.7%) in our study. The main reason for this was that small concomitant lesions were difficult to detect and were overlooked in preoperative examination. It is thus useful to know where in the stomach multiple primary gastric carcinoma tends to occur. Our study indicated that they were located in the lower third of the stomach in high incidence. The correlation between the location of main and concomitant lesions revealed that concomitant lesions were detected in the lower third of the stomach and more often occurred at the distal site of the main lesion than at the proximal site when the main lesion was located in the upper or middle third of the stomach. These results indicate that with distal gastrectomy for multiple primary gastric carcinoma, it is not risky to miss other lesions in the residual stomach. However, with proximal gastrectomy, it is risky to fail to find concomitant lesions in the residual antral region of the stomach. Thus it is necessary to investigate carefully the lower third of the stomach before proximal gastrectomy, especially when the patient has an elevated and well-differentiated adenocarcinoma. Such attention also should be paid in cases of endoscopic resection for early gastric carcinoma. The routine use of fluoroendoscopy [13] with methylene blue or congo red may be a useful diagnostic examination in order to identify incidential small concomitant lesions.

## CONCLUSIONS

The dominant findings of our clinicopathological study of multiple primary gastric carcinoma were an elevated type in gross appearance, papillary or well-differentiated adenocarcinoma histologically, and invasion to the depth of the mucosa. Concomitant lesions incidental to main lesions were mostly detected in the lower third of the stomach and occurred more often at a distal site of the main lesion than at a proximal site when a main lesion was located in the upper or middle third of the stomach. A careful investigation of the lower third of the stomach and the distal site of the main lesion is therefore required

**TABLE VII. Review of Multiple Primary Gastric Carcinoma**

| Reference | No. of patients | No. of lesions (2/3 or >) | Incidence (%) | Male/female | Early/advanced gastric cancer (no. of cases) | Age | Predominant histological type |
|---|---|---|---|---|---|---|---|
| Collins et al. [1] (1952) | 26 | — | 22% | — | — | — | — |
| Moertel et al. [2] (1957) | 40 | 29/9 | 2.18% | 5.7/1 | — | 62/54[a] | — |
| Moertel et al. [2] (1957) (review) | 125 | — | 0.83–2.18% | — | — | — | — |
| Yokoyama et al. [3] (1964) | 62 | 44/18 | 3.7% | — | — | 60–69 | — |
| Baba et al. [4] (1973) | 153 | 110/43 | 6.4% | 3.8/1 | — | — | well differentiated |
| Yasui et al. [5] (1976) | 27 | 23/4 | 3.5% | 3.8/1 | 12/15 | 58 | well differentiated |
| Yamagiwa et al. [6] (1979) | 101 | 86/15 | 5.3% | 2.9/1 | 37/64 | 62 | well differentiated |
| Kumagai [7] (1982) | 77 | 34/10 | 5.1% | 3.9/1 | 44/33 | 61 | differentiated |
| Iwafuchi et al. [8] (1983) | 51 | 45/6 | 9.7% | 2.6/1 | 20/31 | 65.2 | differentiated |
| Yamada et al. [9] (1987) | 42 | 40/2 | 6.5% | 9.5/1 | 20/22 | 60–69 | well differentiated |
| Kosaka et al. [10] (1988) | 49 | 42/7 | 5.8% | 4.4/1 | 26/23 | 63.5 | well differentiated |
| Saitoh et al. [11] (1989) | 49 | 44/5 | 4.4% | 4.4/1 | 35/14 | 62 | well differentiated |
| Furukawa et al. [12] (1992) | 276 | 224/52 | 8.6% | 5.3/1 | ... | 60–69 | — |
| Our study (1996) | 107 | 84/23 | 6.8% | 3/1 | 55/52 | 62 | well differentiated |

[a] Mean age of patients: male/female.

to avoid overlooking incidental concomitant lesions, especially when a patient has the clinicopathological features described above.

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